PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: ROBERT G. WEILACHER
SMITH, GAMBRELL & RUSSELL, LLP
BEVERIDGE, DEGRANDI, WEILACHER & YOUNG
INTELLECTUAL PROPERTY GROUP
1850 M STREET, N.W., SUITE 800
WASHINGTON DC 20036

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	28 JAN 2000
Applicant's or agent's file reference: 33146DC002	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US99/05773	17 MARCH 1999	18 MARCH 1998

Applicant: RISK MANAGEMENT ASSOCIATES LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	NATHAN M. NUTTER DEBORAH THOMAS PARALEGAL SPECIALIST
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0661

Form PCT/IPEA/416 (July 1992)★

RECEIVED
FEB 02 2000
SMITH, GAMBRELL & RUSSELL, L.L.P.

RECEIVED
FEB 0 2 2000
SMITH, GAMBRELL & RUSSELL, L.L.P.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 33146DC002	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US99/05773	International filing date *(day/month/year)* 17 MARCH 1999	Priority date *(day/month/year)* 18 MARCH 1998
International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet.		
Applicant RISK MANAGEMENT ASSOCIATES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

   [✓] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of report with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 OCTOBER 1999	27 NOVEMBER 1999
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NATHAN M. NUTTER DEBORAH THOMAS PARALEGAL SPECIALIST Telephone No. (703) 308-0661

Form PCT/IPEA/409 (cover sheet) (January 1994)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

national application No.
PCT/US99/05773

I. Basis of the report

1. This report has been drawn on the basis of *(Substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments)*:

[X] the international application as originally filed.

[X] the description, pages 1-17 , as originally filed.
pages NONE , filed with the demand.
pages NONE , filed with the letter of _____.
pages _____ , filed with the letter of _____.

[X] the claims, Nos. 1-20 , as originally filed.
Nos. NONE , as amended under Article 19.
Nos. NONE , filed with the demand.
Nos. NONE , filed with the letter of _____.
Nos. _____ , filed with the letter of _____.

[X] the drawings, sheets/~~fig~~ NONE , as originally filed.
sheets/~~fig~~ NONE , filed with the demand.
sheets/~~fig~~ NONE , filed with the letter of _____.
sheets/~~fig~~ _____ , filed with the letter of _____.

2. The amendments have resulted in the cancellation of:

[X] the description, pages NONE.

[X] the claims, Nos. NONE.

[X] the drawings, sheets/~~fig~~ NONE.

3. [ ] This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the ~~Supplemental Box~~ Additional observations below (Rule 70.2(c)).

4. Additional observations, if necessary:

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

[redacted]national application No.
PCT/US99/05773

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-20	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-20	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-20	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-20 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the production and use of rubber products of reduced antigenicity wherein the latex sap is treated with an aldehyde to react with and crosslink the proteins in the sap prior to processing. The products have use in industry in the medical arts.

---------- NEW CITATIONS ----------

NONE

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(6): A61F 6/00; A61L 2/00, 27/00, 31/00; C08F 34/00, 134/00 and US Cl.: 526/295; 528/934, 935; 2/168

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61F 6/00, A61L 2/00, 27/00, 31/00, C08F 34/00, 134/00

A1

(11) International Publication Number: WO 99/47087

(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/US99/05773

(22) International Filing Date: 17 March 1999 (17.03.99)

(30) Priority Data:
60/078,388 18 March 1998 (18.03.98) US

(71) Applicant *(for all designated States except US)*: RISK MANAGEMENT ASSOCIATES LTD. [US/US]; 62 Pointe Rok, Worcester, MA 01604 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: WEINERT, George, W. [US/US]; 62 Pointe Rok, Worcester, MA 01604 (US).

(74) Agents: DEGRANDI, Joseph, A. et al.; Smith, Gambrell & Russell, LLP, The Beveridge, DeGrandi, Weilacher & Young Intellectual Property Group, Suite 800, 1850 M Street, N.W., Washington, DC 20036 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS FOR REDUCING PROTEIN ALLERGENS IN LATEX PRODUCTS

(57) Abstract

Described is a process for reducing the antigenicity of sap and products made from the sap of the *Hevea brasilisensis* plant and other rubber plants. The process involves contacting sap or a latex rubber product with a mono or dialdehyde, a semialdehyde or any chemical containing an aldehyde group, to cross–link antigenic proteins within the sap or the latex product. The cross–linked proteins no longer have the capability to cause an allergic reaction to persons coming into contact with the latex products made by the process of the invention. The cross–linking reaction between the proteins in the latex sap and the aldehyde can take place in the solution used to prepare the final product, or after the final latex product has been formed, or during various intermediate steps of the processes for forming the latex products.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PROCESS FOR REDUCING PROTEIN ALLERGENS IN LATEX PRODUCTS

Reference to Related Application

This application claims priority on U.S. 60/078,388 filed on March 18, 1998 which is incorporated herein in its entirety.

Industrial Applicability

This invention relates to a process for reducing protein allergy caused by latex products, such as latex gloves and latex-containing devices used by the medical profession, which are made from the latex sap of the *Hevea brasilisensis* tree.

Background of the Invention

It is well known that latex products, such as latex gloves, condoms, catheters and automobile tires made from the sap of the *Hevea brasilisensis* tree cause allergic reactions to some individuals who come into contact with such products. The allergic reaction is caused by the water-soluble proteins present in the sap of the tree and in the product made therewith.

In the late 1980s the United States Occupational Safety and Health Administration (OSHA) published *Bloodborne Pathogen Standards* requiring increased use of gloves to protect health care workers from exposure to the AIDS and hepatitis B viruses. Latex glove production substantially increased prior to and following the publication of such *Standards*. In 1991,

the United States Food and Drug Administration (FDA) issued a latex alert regarding allergic reactions of patients and medical personnel who had come in contact with latex products. Among the latex products identified as potentially hazardous by the FDA were surgeon's gloves, latex exam gloves, latex condoms, barium enema retention rings and Foley catheters. The latex alert was issued after the number of annual cases regarding allergic reactions resulting from latex products increased from a few to 1,600. Of the three types of latex related diseases - dermatitis, cell mediated allergy and systemic allergy - which manifest themselves through different symptoms, cell mediated allergic response is a true allergic response, with reaction restricted to the area of contact between the glove and the skin when the glove is made from the sap of the *Hevea brasilisensis* tree. The reaction may include swelling and blistering and, after washing of the hands upon removal of the gloves, it takes from about 24 to 48 hours for the person's skin to return to normal. This allergy is caused by several water soluble proteins in latex sap.

Systemic latex allergy, the most serious of the latex-related diseases, is characterized by allergic rhinitis - asthma - and can escalate to anaphylaxis and death. This allergy is caused by several water soluble proteins in the latex sap from the *Hevea brasilisensis* tree present in products made from such sap, which proteins are dispersed in the air and are breathed in by people. Methods of measurement

of airborne concentrations of latex antigen as well as latex antigen concentrations in products, such as gloves, in amount as low as 1 nanogram per cubic meter (ng/M^3) are known. Several healthcare institutions have decided to adopt 10 ng/M^3 as a ceiling concentration or standard for personal exposure.

It is known that up to 100 percent of the water soluble protein can be removed from latex of the *Hevea brasilisensis* tree by subjecting the latex to several washings with water and to centrifugation, but with each washing the latex yield decreases, thus increasing the cost of the resulting purified product. Numerous attempts have been made by others to solve the problem of allergic reactions caused to certain people when they come into contact with rubber products made from the sap of the *Hevea brasilisensis* tree due to the proteins in the sap being present in such products.

U.S. Patent No. 5,580,942 acknowledges the severe allergic reactions in hypersensitive people caused by the proteins present in the natural rubber latex obtained from *Hevea brasilisensis* trees. The patentee has a simple solution to the problem, namely, avoiding use of the latex from the *Hevea brasilisensis* in making latex products. Instead, the patentee uses latex extracted from the Parthenium argontatum (guayule) plant or the Ficus elastica plant, which plants have a different protein profile, whereby the proteins from the sap of these plants do not cause allergic reactions in hypersensitive humans.

A review of latex measurement proteins has been published (Beezhold D.H., Measurement of latex proteins by chemical and immunological methods, Procedings of Latex Protein Allergy: The Present Position. Amsterdam, Dec. 1993).

Proteins have been isolated from rubber particles and from the B and C serum fractions of fresh non-ammoniated latex (NAL). When analyzed by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE), distant protein bands are observed (Hasma, *J. Nat. Rubb. Res.*, 1992, 7(2), 102-112; Arreguin, et al., Electrophoresis, 1988, 9, 323-326; Slater, et al., *J. Allergy, Clin. Immunolo.*, 1992, 89, 673-678.). Electrophoretic profiles of NAL reveals major proteins at 46, 29 and 14kDa, and minor bands at 90, 55, 40, 36, 24, 20 and 18kDa. Hevein (4kDa) and hevamine (29kDa) are two proteins in latex sera which have been cloned and sequenced (Lee et al., *Biol Chem.*, 1991, 256, 15944-15948; Jekel et al., *Eur. J. Biochem.*, 1991, 200, 123-130). In addition, rubber particles contain the tightly bound proteins prenyltransferase (38kDa) and rubber elongation factor (14.5kDa) which have also been sequenced (Dennis et al., *Biol. Chem.*, 1989, 264, 18618-26; Light et al., *J. Biol. Chem.* ,1989 264, 18589-97).

Ammonification of latex alters the proteins. Storage of latex in ammonia alters the electrophoretic profiles of proteins such that SDS-PAGE profile changes from distinct bands to a smear of polypeptides with an increase in high molecular weight material (Breezhold et al., *Arch. Surg.*,

1992, 127, 1354-1357). Many, but not all, of the changes that occur are due to hydrolysis of the proteins. Since NAL serum proteins migrate primarily below 46kDa, the appearance of high molecular weight polypeptides suggests that ammonification (and/or other compounding ingredients) induce a type of polymerization of the latex proteins that produces the larger polypeptides. This process may contribute to the allergenicity of the latex proteins. In addition, ammonification also extracts some of the rubber bound proteins (primarily rubber elongation factor) making them soluble proteins and thus potential allergens (Hasma, *J. Nat. Rubb. Res.*, 1992, 7(2), 102-112).

Much of the protein in latex is not tightly bound to the rubber, but is "water soluble" and readily leaches out of the latex. In order to measure latex proteins it is important to understand the parameters which influence extractability. It has been shown that water soluble proteins are readily extractable, however, complete extraction may take up to 18 hours or more (Dalrymple et al., *Rubb. Devel.*, 1992, 45, 51-60; Hashim, *International Rubber Technology Conference*, Kuala Lumpur, Malaysia, June 1993; Yeang et al., *International Rubber Technology Conference*, Kuala Lumpur, Malaysia, June 1993). The volume, pH, and composition of extraction buffer are also important factors.

A majority of the latex proteins have an acidic pH between 4.0 and 6.5 (Chambeyron et al., *Allergy*, 1992, 90, 230-235) that increases their solubility in basic buffers and helps explain the observation that more protein is extracted in higher pH buffers. Latex proteins are drawn to the surface of the latex during drying. The surface proteins can be collected directly from the surface by dry swabbing (Dalrymple et al., *Rubb. Devel.*, 1992, 45, 51-60). By analyzing proteins obtained from dry swabbing rubber films, a unique group of surface proteins which are nearly insoluble in water and have limited solubility in carbonate buffer was observed. These proteins migrate in SDS gels with a relative molecular mass of between 60 and 70kDa. The proteins are remarkable in that they can be identified by their ability to non-specifically bind IgM from human serum. Furthermore, the IgM binding proteins (IgMbp) can activate the serum complement system and thereby have the potential to cause anaphylactoid reactions. Because these proteins are insoluble they are easily overlooked but must be considered as a potential source of allergens.

Attempts to identify specific allergens has resulted in a wide range of different molecular weight allergens being proposed (Chambeyron, et al., *Allergy*, 1992, 47, 92-97; Makinen-Kiljunen et al., *J. Allergy Clin. Immunol.*, 1992,90, 230-235; Jaeger et al., *Allergy Clin. Immunol.*, 1992, 89,

759-768). A recent review summarized the published data and suggested that the studies implicate two proteins of 30kDa and 14kDa as the common allergens (Hamann, *Amer. J. Cont. Derma.*, 1993, 4, 4-21). An abstract recently identified a 14kDa allergen as rubber elongation factor, one of the rubber bound proteins (Czuppon et al., CHEST 104; abstract 159S, 1993).

U.S. Patent No. 5,610,212 acknowledges that products made of natural rubber, such as rubber gloves, produce allergic reactions in some people, which reactions are attributed to the proteins present in natural rubber. The patent also discusses prior deproteinizing processes for latex which have been used to get around the problem caused by natural rubber. The patent discloses a process for markedly improving the stabilization of deproteinized natural rubber latex which has been treated with a protease and a surfactant, by addition thereto of a specific surfactant or an oligomer or polymer.

U.S. Patent No. 5,622,998 discusses various known processes for depolymerizating natural rubber and discloses a process for forming a liquid depolymerized natural rubber which produces no immediate allergy. The patentee dissolves a deproteinized natural rubber into an organic solvent to a concentration of about 1 to 30 percent by weight and then carries out air oxidation of the resulting solution in the presence of a metallic catalyst.

Brief Summary of the Invention

The process of the invention comprises reacting proteins in the sap of the *Hevea brasilisensis* plant and other rubber plants, which sap is used in the known processes for the manufacture of latex products, such as latex gloves or other latex-containing products, automobile tires and medical devices which are intended to come into contact with people or will be exposed to people, such as patients, doctors, nurses, laboratory technicians and others, with an aldehyde, such as a mono-aldehyde, such as formaldehyde, or a dialdehyde, such as glutaraldehyde or semialdehydes or any chemical containing an aldehyde group, to cross-link such proteins. The cross-linked proteins no longer have the capability to cause an allergic reaction to persons coming into contact with the latex products made by the process of the invention. The cross-linking reaction between the proteins in the latex sap and the aldehyde can take place in the solution used to prepare the final product, or after the final latex product has been formed, or during various intermediate steps of the known processes for forming the latex products.

Detailed Description of the Invention

The invention comprises a process for significantly reducing and/or eliminating the allergy caused to certain people who come into contact with latex products made from the latex sap of the *Hevea brasilisensis* plant or any latex

producing plant due to the presence of proteins from the latex sap. Processes for making such latex products are well known. Applicant has found that he can significantly decrease and/or even eliminate the presence of these proteins in the sap which causes the allergic reactions by reacting such proteins with an aldehyde, such as formaldehyde, or preferably with a di-aldehyde, most preferably, glutaraldehyde. Such reaction can take place in the latex solution used in a step of the known process of making the latex product. Such aldehyde, and preferably glutaraldehyde, is added to and stirred in the latex solution in an amount sufficient to react with the proteins in the latex solution and to cross-link substantially all of the proteins into polymers. Alternatively, the reaction between the proteins in the sap of the latex and the aldehyde can take place during other steps in the known processes for making the latex products, as long as the proteins in the latex come into contact with and react with the aldehyde and are cross-linked to form a polymer. Such reaction can also take place after the latex product, such as the rubber glove, is formed. The reaction of the proteins in the latex which are on the surfaces of the latex product are reacted with the aldehyde, such as by the coating of the surface with the aldehyde, or by the immersion of the product in the aldehyde, for a period of time sufficient to completely react and cross-link the proteins with the aldehyde.

The use of an aldehyde and, particularly, glutaraldehyde, to obtain the significant reduction of protein allergies caused by latex products made from the sap of the *Hevea brasilisensis* tree is contrary to what one would be expected to use. Glutaraldehyde is one of two high-level disinfectant chemicals currently approved by the FDA for disinfecting endoscopes, bronchoscopes, cystoscopes, ultrasonic transducers and other devices not amenable to disinfection by heat, steam, radiation or other means. Glutaraldehyde presents a health hazard to persons working with it, such as red burning eyes, sore throat, nasal discharge and red itchy skin. Glutaraldehyde is also a skin sensitizer and has been known to aggravate asthma. Applicant has found that by reacting two known health hazards to humans, namely, the proteins in the latex sap of the *Hevea brasilisensis* tree and glutaraldehyde, the proteins cross-linked with the glutaraldehyde form a reaction product which eliminates the protein allergy of the latex product.

The latex with reduced allergans that is produced by the method of the invention will result in significantly increased safety for latex allergic persons who use or are exposed to the following types of latex containing products:

<u>Emergency Equipment</u>

Blood pressure cuffs, stethoscopes, disposable gloves, oral and nasal airways, endotracheal tubes,

tourniquets, intravenous tubing, syringes and electrode pads

Personal Protective Equipment

Gloves, surgical masks, goggles, respirators and rubber aprons

Office Supplies

Rubber bands and erasers

Hospital Supplies

Anesthesia masks, catheters, wound drains, injection ports, rubber tops of multidose vials and dental dams

Consumer Products

Automobile tires, motorcycle and bicycle handgrips, carpeting, swimming goggles, racquet handles, shoe soles, expandable fabric (waistbands), dishwashing gloves, hot water bottles, condoms, diaphragms, balloons, pacifiers, and baby bottle nipples

The following examples are merely illustrative of the process of the invention.

The radio-immunosorbant assay (RAST) is often used as a sensitive technique which employs radio-isotope labelled anti-IgE to measure specific IgE antibody in patient sera. The latex RAST (Pharmacia) is used to determine if specific IgE to the latex proteins is present and is semi-quantitative in

determining the amount of IgE present. The assay is used primarily as a diagnostic test for latex allergy.

The RAST assay employed below is performed as a competition assay (RAST inhibition) to quantitate the amount of allergen in a latex extract. In this assay, soluble allergens in latex extracts compete for binding to latex specific IgE in pooled sera from latex allergic individuals. When soluble allergens react with the IgE, the antibody is prevented from binding to a solid phase latex allergen preparation. The amount of inhibition reflects the level of soluble allergens in the extract. The RAST inhibition assay is a very sensitive method to quantitate latex allergens.

Examples of Latex Allergan Reduction by the Process of the Invention

Example 1.

1. Ammoniated latex (C.N.L from the General Latex and Chemical Corporation, Billerica, MA) was treated with glutaraldehyde and formaldehyde to effectively cross-link the natural rubber proteins. 20 cc of a 20 % glutaraldehyde solution (Sigma Chemical, St Louis, MO, #G6257) were added to 700 cc of latex sap. 22 cc of a 37% solution of formaldehyde (Fisher Chemical, Fair Lawn, NJ) were added to 700 cc of latex sap. Both experiments and a control of latex sap were conducted at room temperature, which was 23 degrees centigrade (C). Ten minutes later, the formaldehyde-latex solution became gel like,

indicating the cross-linking of protein had occurred. The glutaraldehyde-latex solution did not become gel-like.

2. The glutaraldehyde-latex solution was coated on a glass plate and allowed to air dry (23 degrees C for 30 minutes). A control of the untreated latex was applied to another glass plate in a similar fashion and allowed to air dry (23 degrees C for 30 minutes). The plates were incubated at 130 degrees C for 30 minutes.

3. The formed films were sent to the MAYO clinic to determine the concentration antigen by the RAST inhibition test, a test specific to measure the antigenic proteins. The control sample contained 409,140 nanograms per gram of antigenic protein, and the glutaraldehyde treated latex sample contained 42,672 nanograms per gram of antigenic protein.

4. Subsequent samples were prepared in a similar fashion described above, except the vulcanization temperature was 120 degrees centigrade. The RAST inhibition antigen testing was conducted at the IBT Reference Laboratory. The control sample contained 13.0 micrograms per gram of antigenic protein, and the glutaraldehyde treated latex sample contained 5.6 micrograms per gram of antigenic protein.

Example 2.

Additional experiments were conducted using a new sample of latex and several other aldehydes.

1. Ammoniated latex (C.N.L. from the General Latex Corporation, Billerica, MA) was treated with formaldehyde and glutaraldehyde as confirmation of earlier experimental tests demonstrating the crosslinking of the natural rubber proteins previously discussed. In addition, samples of the latex were treated with, citronellal (Fisher Scientific, Pittsburgh, PA, #AC405291000), butyraldehyde (Fisher Scientific, Pittsburgh, PA, # AC220302500) and crotonaldehyde (Fisher Scientific, Pittsburgh, PA #AC 158220050). An aliquot of each aldehyde was added to 20 milliliters of latex dispersion. All five experiments were conducted at room temperature, which was 22 degrees centigrade (C). There was no apparent thickening in any of the five solutions.

2. Each solution was coated on a glass plate and allowed to air dry for 30 minutes at 22 degrees centigrade (C). The plates were incubated for 20 minutes at 200 degrees Fahrenheit

3. The formed films were sent to the MAYO Clinic to determine the concentration of antigen by the RAST inhibition test, a test specific to measure antigenic proteins. This control sample contained 9370 nanograms per gram of antigenic protein.

4. 400 microliters of formaldehyde were added to 20 milliliters of latex. The sample contained 2249 nanograms per gram of antigenic protein. This was a 76 percent reduction as compared to the control sample.

5. 800 microliters of glutaraldehyde were added to 20 milliliters of latex, and the sample contained 5254 nanograms per gram of antigenic protein. This was a 44 percent reduction as compared to the control sample.

6. 800 microliters of butyraldehyde were added to 20 milliliters of latex, and the sample contained 1461 nanograms per gram of antigenic protein. This was an 84 percent reduction as compared to the control sample.

7. 400 microliters of crotonaldehyde were added to 20 milliliters of latex, and the sample contained 5554 nanograms per gram of antigenic protein. This was a 41 percent reduction as compared to the control sample.

8. 200 microliters of citronellal were added to 20 milliliters of latex, and the sample contained 4515 nanograms per gram of antigenic protein. This was a 52 percent reduction as compared to the control sample.

Example 3.

Examples of Latex Allergan Reduction in a Typical Manufacturing Process

A typical manufacturing sequence for a dipped product such as a glove or a condom involves sequential steps of:

1. dipping a form or mandrill into a release agent
2. air drying the release agent coated form or mandrill
3. dipping the form or mandrill into a latex solution
4. air drying the latex coated form or mandrill
5. vulcanizing the latex, and generally,
6. dipping the vulcanized product a dispersion of powder

The product is then stripped from the form or mandrill and packaged. Some products, such as surgical gloves, may also be sterilized, usually by radiation.

The method of the invention can be performed at different steps of the manufacturing process. The aldehyde solution can be mixed with the latex dipping solution. Generally the aldehyde is added to the latex solution with mixing to promote uniformity. The aldehyde can also be in line blended with the latex solution to maintain a consistent depth of the dipping solution. Currently, some glove manufactures spray water on the vulcanized glove to wash away water-soluble surface protein or pass the gloves on the mandrills through a series of leaching tanks. By the method of the invention, the aldehyde can be added to the washing or leaching solutions or could

be sprayed directly onto the finished product to cross-link the surface proteins.

The above examples demonstrate that substantial reductions in latex antigens can be obtained by the method of the invention.

Further variations and modifications will be apparent to those skilled in the art and are intended to be encompassed by the claims appended hereto.

I CLAIM:

1. A process for reducing the antigenicity of proteins in latex sap comprising:

contacting a sufficient amount of an aldehyde with an antigenic latex protein to react with and cross-link the protein so as to significantly reduce the antigenicity of the protein.

2. A process for reducing the antigenicity of proteins in latex sap comprising:

forming a solution of a latex sap containing an antigenic protein, and

adding a sufficient amount of an aldehyde to react with and cross-link the protein so as to significantly reduce the antigenicity of the protein.

3. A latex sap produced by the process according to claim 2.

4. The process as defined in Claim 1, wherein said aldehyde is a mono-aldehyde or a dialdehyde.

5. The process as defined in Claim 3, wherein said dialdehyde is glutaraldehyde.

6. The process as defined in Claim 3, wherein said mono-aldehyde is formaldehyde.

7. A process for making a latex product with reduced antigenicity from latex sap containing antigenic proteins, comprising:

forming a solution of said latex sap,

applying a sufficient amount of an aldehyde to a surface of the product to react with and cross-link the protein so as to significantly reduce the antigenicity of the protein,

shaping said latex sap into a product, and

vulcanizing said product.

8. The process as defined in Claim 7, wherein said aldehyde is a mono-aldehyde or a dialdehyde.

9. The process as defined in Claim 8, wherein said dialdehyde is glutaraldehyde.

10. The process as defined in Claim 8 wherein said mono-aldehyde is formaldehyde.

11. A process for making a latex product with reduced antigenicity from latex sap containing antigenic proteins, comprising:

forming a solution of said latex sap,

shaping said latex sap into a product,

vulcanizing said product, and

applying a sufficient amount of an aldehyde to a surface of the product to react with and cross-link the protein so as to significantly reduce the antigenicity of the protein.

12. The process as defined in Claim 11, wherein said aldehyde is a mono-aldehyde or a dialdehyde.

13. The process as defined in Claim 12, wherein said dialdehyde is glutaraldehyde.

14. The process as defined in Claim 12 wherein said mono-aldehyde is formaldehyde.

15. A latex product produced by the process according to claim 7.

16. A latex product produced by the process according to claim 11.

17. In a process for making a latex product from the latex sap of the *Hevea brasilisensis plant* containing antigenic proteins which cause allergic reactions to persons coming into contact with said latex product, comprising;

forming a solution of said latex sap, shaping said latex sap into a product and vulcanizing said product, the improvement comprising the step of reacting said proteins

present in said latex sap with a sufficient amount of an aldehyde to react with and cross-link said proteins, so as to significantly reduce the allergenicity of said latex product.

18. The process as defined in Claim 17, wherein said aldehyde is a mono-aldehyde or a dialdehyde.

19. The process as defined in Claim 18, wherein said dialdehyde is glutaraldehyde.

20. The process as defined in Claim 18, wherein said mono-aldehyde is formaldehyde.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05773

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 6/00; A61L 2/00, 27/00, 31/00; C08F 34/00, 134/00
US CL :526/295; 528/934, 935; 2/168
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 526/295; 528/934, 935; 2/168

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,691,446 A (DOVE) 25 November 1997, see entire document.	1-20
A,P	US 5,741,885 A (DOVE) 21 April 1998, see entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 30 APRIL 1999	Date of mailing of the international search report 20 MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NATHAN M. NUTTER Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet)(July 1992)★

RECEIVED
OCT 04 1999
SMITH, GAMBRELL & RUSSELL, L.L.P.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/05773

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61F 6/00; A61L 2/00, 27/00, 31/00; C08F 34/00, 134/00
US CL :526/295; 528/934, 935; 2/168

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 526/295; 528/934, 935; 2/168

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,691,446 A (DOVE) 25 November 1997, see entire document.	1-20
A,P	US 5,741,885 A (DOVE) 21 April 1998, see entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 APRIL 1999	20 MAY 1999
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer NATHAN M. NUTTER Telephone No. (703) 308-0661

Form PCT/ISA/210 (second sheet)(July 1992)★

RECEIVED
OCT 04 1999
SMITH, GAMBRELL & RUSSELL, L.L.P.